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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 213/02, 401/06, 405/06, 409/06, 411/06, 413/06, A61K 31/44

A1

(11) International Publication Number: WO 94/22830

(43) International Publication Date: 13 October 1994 (13.10.94)

(21) International Application Number: PCT/US94/03478

(22) International Filing Date: 30 March 1994 (30.03.94)

(30) Priority Data:
08/040,733 31 March 1993 (31.03.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/040,733 (CON)
Filed on 31 March 1993 (31.03.93)

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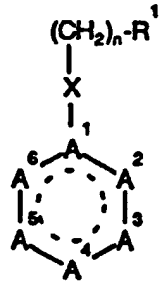
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CHEMICAL COMPOUNDS

(57) Abstract

Angiotensin II receptor antagonists having formula (I) which are useful in the treatment of hypertension, congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.



(I)

small amount of
slope overlap
different therapeutic area
no anticipation

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CHEMICAL COMPOUNDS

The present invention relates to new chemical compounds which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

BACKGROUND OF THE INVENTION

The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (AII), being one of the most potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in cardiovascular hemeostasis.

Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), Federation Proc., 43, 1314). The most direct approach towards inhibition of the renin-angiotensin system would block the action of AII at the receptor. Compelling evidence suggests that AII also contributes to renal vasoconstriction and sodium retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), J. Cardiovas. Pharmacol., 6, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), J. Clin. Invest., 76, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that AII antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

The compounds of this invention inhibit, block and antagonize the action of the hormone AII, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders

attributed to the actions of AII. When compounds of this invention are administered to mammals, the elevated blood pressure due to AII is reduced and other manifestations based on AII intercession are minimized and controlled. Compounds of this invention are also expected to exhibit diuretic activity.

Recognition of the importance of blocking and inhibiting the actions of AII has stimulated other efforts to synthesize antagonists of AII. The following references have disclosed imidazole derivatives which are described as having AII blocking activity and useful as hypotensive agents.

Furukawa et al., U.S. Patent 4,340,598 discloses imidazol-5-yl-acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

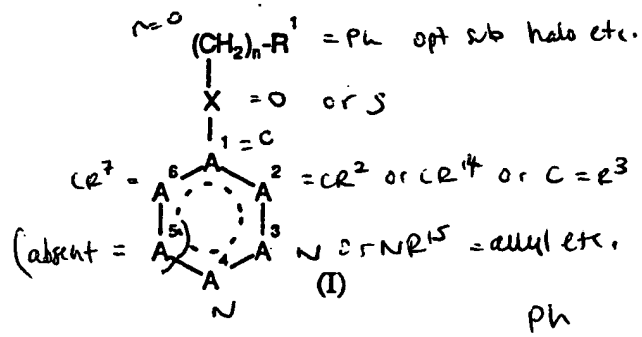
Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

Carini et al. in EP 253,310 disclose certain imidazolylpropenoic acids. Two intermediates described in this patent are ethyl 3-[1-(4-nitrobenzyl)-2-butyl-4-chloroimidazol-5-yl]propenoate and ethyl 3-[2-butyl-4-chloro-1-(4-aminobenzyl)imidazol-5-yl]propenoate.

Also, Wareing, in PCT/EP 86/00297, discloses as intermediates certain imidazolylpropenoate compounds. On page 62, Formula (CX) is ethyl 3-[1(-4-fluorophenyl)-4-isopropyl-2-phenyl-1H-imidazol-5-yl]-2-propenoate.

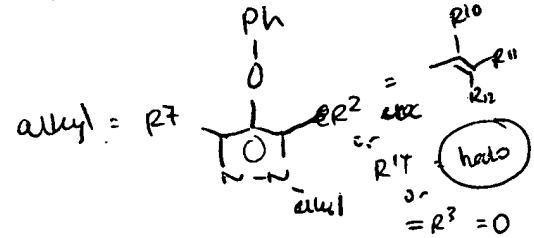
DESCRIPTION OF THE INVENTION

The compounds of the present invention that are blockers of angiotensin II receptors are represented by the following Formula (I):



(I)

wherein:



R^1 is phenyl or naphthyl, each of which is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_{1-6}alkyl, NO_2, CF_3, Q-CO_2R', tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR', $NHSO_2R''$, SO_3H, CONR'R', CN, SO_2C_{1-6}alkyl, NR'R', NR'COH, NR'COC_{1-6}alkyl or NR'CO-phenyl;

n is 0-4;

A^1 is C or N when X is a covalent bond, or C when X is other than a covalent bond;

A^2 is CR^2, CR^{14}, or $C{=}R^3$;

A^3 is CR^2, CR^4, N, or NR^{15};

A^4 is CR^5, CR^5R^9, or N;

A^5 is absent or present as CR^6 or N;

A^6 is CR^7 when A^5 is absent or CR^8 or N when A^5 is present;

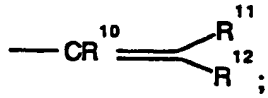
with the proviso that:

(1) one of A^2 or A^3 is CR^2; and

(2) at least one, but not more than three of A^1, A^3, A^4, A^5 and A^6 are N;

each R' independently is H or C_{1-6}alkyl;

R'' is R', C_mF_{2m+1}, wherein m is 1-3, or phenyl which is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_{1-6}alkyl, NO_2, CF_3, Q-CO_2R', tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR', $NHSO_2R'$, SO_3H, CONR'R', CN, SO_2C_{1-6}alkyl, NR'R', NR'COH, NR'COC_{1-6}alkyl or NR'CO-phenyl;

R^2 is  ;

R^3 is O, (H,H), or (H, C_{1-4}alkyl);

R^4 is H, C_{1-4}alkyl, Cl, Br, F, or I;

R^5 is H, C_{1-4}alkyl, Cl, Br, F, or I;

R^6 is H or C_{1-4}alkyl;

R^7 is C_{2-8}alkyl, SC_{1-7}alkyl or OC_{1-7}alkyl;

R^8 is H, C_{2-8}alkyl, SC_{1-7}alkyl, or OC_{1-7}alkyl;

each R^9 independently is H or C_{1-6}alkyl;

R^{10} is H or C_{1-6}alkyl;

R^{11} is CO_2R', CONR'R', tetrazolyl, or SO_2NH_2;

R^{12} is C_1-C_6alkyl, phenyl-Y-, biphenyl-Y-, naphthyl-Y-, 2- or 3-thienyl-Y-, 2- or 3-furanyl-Y-, 2-, 3- or 4-pyridyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-,

triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, or tetrazolyl-Y-, with each heteroaryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR'R', CO_2R', SO_2NHR', SO_3H, CONR'R', OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR'COH, or NR'COC$_1$-C_6alkyl and with each aryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR'R', CO_2R', SO_2NHR', SO_3H, CONR'R', OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR'COH, or NR'COC$_1$-C_6alkyl or with each aryl group being substituted by methylenedioxy, phenoxy, or phenyl;

Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched optionally substituted by phenyl or benzyl, wherein each phenyl or benzyl group is unsubstituted or substituted by Cl, Br, F, I, NO_2, CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, CN, or CO_2R';

Q is -CH=CH-, -$(CH_2)_{0-4}$-, -X-$(CH_2)_{1-2}$-U-$(CH_2)_{1-2}$-, or -V-CH(R^{13})-;

X is a covalent bond, -O-, -S-, or -N(R^9)-;

U is absent or present as -O-, -S-, or -N(R^9)-;

V is -O-, -S-, or -N(R^9)-;

R^{13} is H, phenyl, or benzyl wherein each phenyl or benzyl group is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_{1-6}alkyl, NO_2, CF_3, Q-CO_2R', tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR', NHSO_2R", SO_3H, CONR'R', CN, SO_2C_{1-6}alkyl, NR'R', NR'COH, NR'COC_{1-6}alkyl or NR'CO-phenyl;

R^{14} is Cl, Br, F, or I; and

R^{15} is H, C_{1-6}alkyl, -$(CH_2)_{1-2}C_{3-6}$cycloalkyl, -$(CH_2)_{1-2}CF_3$, or -$(CH_2)_{0-2}$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

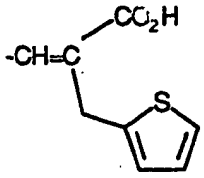
As used herein, the terms alkyl and alkoxy mean carbon chains which are branched or unbranched with the length of the chain determined by the descriptor preceding the term. The phrase "any accessible combination" means any combination of substituents that is available by chemical synthesis and is stable.

Aryl, as used herein, means phenyl, biphenyl, or naphthyl. Heteroaryl means 2- or 3-thienyl-Y-, 2- or 3-furanyl-Y-, 2-, 3- or 4-pyridyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, or tetrazolyl-Y-.

As used herein, ⎓ indicates a single or double bond, wherein the A^1-A^6 ring contains two or three double bonds.

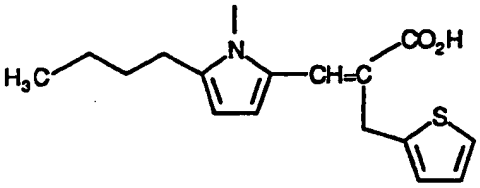
Presently preferred Formula (I) compounds are those compounds wherein R^1 is phenyl or naphthyl, each of which is substituted by Q-CO_2R', CONR'R', $NHSO_2R''$, or tetrazolyl. The most preferred substituent on the R^1 phenyl or naphthyl is 4-CO_2H. Also, Formula (I) compounds wherein n is one are most preferred.

Another preferred embodiment are Formula (I) compounds wherein R^2 is

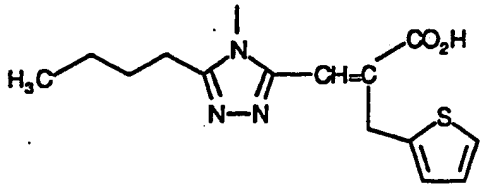


in which the A^1 - A^6 ring and the CO_2H group are trans to each other (the E isomers). These isomers are generally more active and, thus, are preferred over the corresponding cis isomers (the Z isomers).

The most preferred A^1-A^6 rings to which X is attached at A^1 are represented by the following:



(1)



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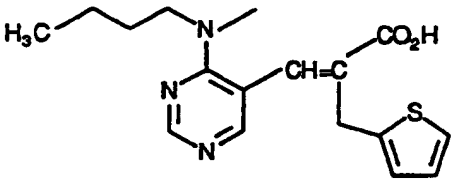

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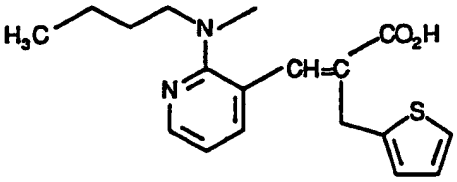

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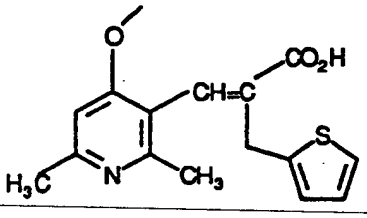

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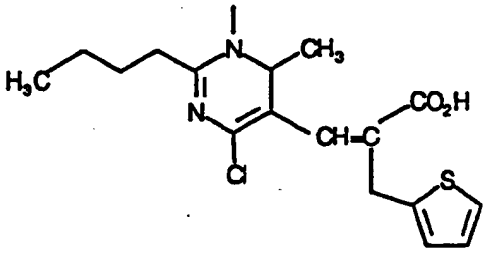

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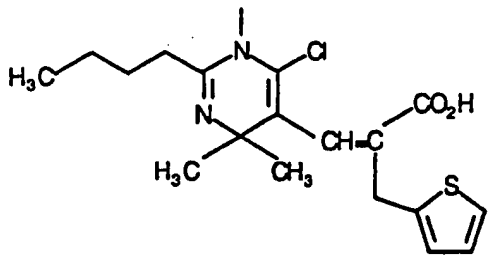
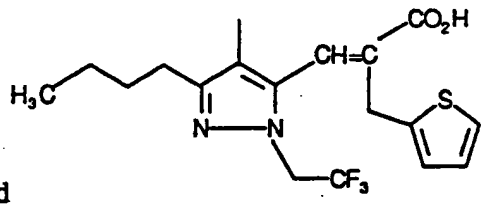


(7)

and



(8)

The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an effective amount of a compound of Formula (I).

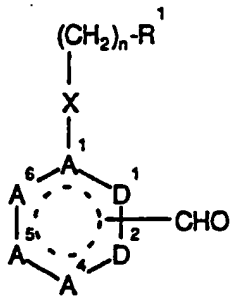
Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I). Methods of treating hypertension, congestive heart failure, glaucoma, and renal failure by administering these compounds are also included in this invention.

Because the compounds of Formula (I) are angiotension II receptor antagonists, they may also be of value in the treatment of left ventricular hypertrophy regression, diabetic nephropathy, diabetic retinopathy, macular degeneration, haemorrhagic stroke, angina, and anxiety. Additionally, these compounds may be expected to be useful in the primary and secondary prevention of infarction, in the prevention of atheroma progression and in the regression of antheroma, in the prevention of restinosis after angioplasty or bypass surgery and in the improvement of cognitive funtion.

The compounds of this invention are prepared by procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the A^1 - A^6 ring and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the functional groups and the protecting groups on the naphthalene and other parts of the molecule.

The compounds of Formula (I) or pharmaceutically acceptable salts thereof are prepared by a process which comprises:

a) reacting a compound of the formula (II):



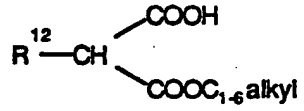
(II)

wherein A^1, A^4, A^5, A^6, and n are as defined in Formula (I), $R^{1'}$ is R^1 as defined in claim 1, except that the substituents on the $R^{1'}$ group do not include tetrazol-5-yl, OH, or CO_2H, and D^1 is C or CH substituted by CHO and D^2 is CR^4, N, or NR^{15} wherein R^4 and R^{15} are as defined in Formula (I), or D^1 is CR^{14} or $C{=}R^3$ and D^2 is C substituted by CHO, wherein R^{14} and R^3 are as defined in Formula (I), with a compound of formula (III):

$$(C_{1-4}\text{alkoxy})_2P(O)CH(R^{12})\text{-}CO_2C_{1-6}\text{alkyl} \qquad \text{(III)}$$

wherein R^{12} is as defined in Formula (I), in the presence of a base; or

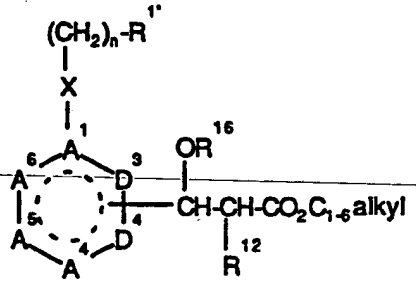
b) reacting a compound of the formula (II) as hereinbefore defined with a compound of the formula (IV):



(IV)

wherein R^{12} is as defined in Formula (I), in the presence of a base; or

c) reacting a compound of the formula (V):



(V)

wherein A^1, A^4, A^5, A^6, and n are as defined in Formula (I), $R^{1'}$ is R^1 as defined in claim 1, except that the substituents on the $R^{1'}$ group do not

include tetrazolyl-5-yl, OH, or CO_2H, and D^3 is C or CH substituted by $-CH(OR^{16})-CH(R^{12})-CO_2C_{1-6}$alkyl and D^4 is CR^4, N, or NR^{15} wherein R^4 and R^{15} are as defined in Formula (I), or D^3 is CR^{14} or $C=R^3$ and D^4 is C substituted by $-CH(OR^{16})-CH(R^{12})-CO_2C_{1-6}$alkyl , wherein R^{14} and R^3 are as defined in Formula (I), and R^{16} is $COCH_3$ or SO_2CH_3, with a base;

and thereafter where necessary:

(i) for Formula (I) compounds in which the R^1 group is substituted by hydroxy, deprotecting the Formula (I) compounds in which the R^1 group is substituted by C_{1-4}alkoxy; or

(ii) for Formula (I) compounds in which the R^1 group is substituted by carboxy, hydrolyzing the Formula (I) compounds in which the R^1 group is substituted by CO_2C_{1-4}alkyl; or

(iii) for Formula (I) compounds in which R^1 group is substituted by a tetrazol-5-yl group, treating the Formula (I) compound in which the R^1 group is substituted by carboxy, with a halogenating agent, followed by conversion to the priary amide in a reaction with ammonia, dehydration with oxalylchloride/dimethylformamide and reaction with azide; or

(iv) for Formula (I) compounds in which R^{11} is CO_2H, hydrolyzing the Formula (I) compounds in which R^{11} is CO_2C_{1-6}alkyl; or

(v) for Formula (I) compounds in which R^{11} is CONR'R' wherein R' is as defined in Formula (I) treating the Formula (I) compounds in which R^{11} is CO_2H with a halogenating agent, followed by reaction with a R', R'-substituted amine; or

(vi) for Formula (I) compounds in which R^{11} is tetrazolyl, treating the Formula (I) compounds in which R^{11} is $CONH_2$ with oxalyl chloride/dimethylformamide, followed by reaction with azide;

and thereafter optionally forming a pharmaceutically acceptable salt.

The reaction between a compound of formula (II) and a compound of formula (III) is performed in the presence of a suitable base, such as a metal alkoxide, lithium hydride or preferably sodium hydride, in a suitable solvent, such as ethanol, methanol, ether, dioxane, tetrahydrofuran, or preferably glyme, at a reaction temperature of about 10°C to about 50°C, preferably at about 25°C, to provide a variable mixture of trans and cis, e.g., (E) and (Z), $-CH=C(R^{12})-(CO_2C_{1-6}$alkyl)-substituted Formula (I) compounds. These isomers are readily

separated by chromatography over silica gel in suitable solvent systems, preferably hexane in ethyl acetate mixtures. The esters are hydrolyzed to the corresponding acids using base, such as potassium hydroxide, lithium hydroxide or sodium hydroxide, in a suitable solvent system, such as, for example, aqueous alcohol or diglyme.

The reaction between a compound of formula (II) and a compound of formula (IV) is performed in the presence of a base, such as piperidine, in a suitable solvent, such as toluene, at a temperature of about 80°C to about 110°C preferably at about 100°C. The resulting -CH=C(R^{12})CO_2C_{1-6}alkyl-substituted Formula (I) compounds are hydrolyzed to the corresponding Formula (I) acid compounds by alkaline hydrolysis as described above.

The reaction between a compound of formula (V) and a base, such as one to two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene, is carried out in a suitable solvent, such as toluene, at about 50°C to about 110°C, preferably at about 80°C, to afford the Formula (I) vinyl ester compounds. The corresponding carboxylic acids are prepared from the esters by the method detailed above.

Formula (V) compounds are prepared from formula (II) compounds. The aldehyde group of formula (II) compounds are treated with the lithium derivative of a substituted ethyl or methyl ester. These lithio derivatives are prepared from the reaction of lithium diisopropylamide in a suitable solvent, preferably tetrahydrofuran, with an acid ester, such as ROOC-CH_2-Y-(2-thienyl), to generate the α-lithio derivatives at about -78°C, which are then treated with the Formula (II) aldehyde. The intermediate ß-hydroxy group of the imidazole ester is converted to a mesylate or an acetate, for example, by reacting the alcohol with methanesulfonyl chloride in pyridine at 0°C to 25°C or by reacting the alcohol with acetic anhydride, to give Formula (V) compounds.

Formula (II) compounds are known in the art or can be made by analogy processes using standard procedures of organic chemistry. For example, the R^1-$(CH_2)_n$- group is incorporated onto the A^1-A^6 ring by reaction with a R^1-$(CH_2)_n$ halide, mesylate or acetate, such as 4-carbomethoxybenzyl bromide or methyl 4-bromomethylnaphthalene-1 carboxylate, in the presence of a suitable acid acceptor, such as sodium alkylate, potassium or sodium carbonate, or a metal hydride, preferably sodium hydride, at a reaction temperature of about 25°C to about 100°C, preferably at about 50°C.

The various formula (II) aldehyde compounds, or the hydroxymetyl precussors thereof, may be prepared employing the methods detailed in the publications hereinbelow and reference should be made to such publications for

their disclosure, which are incorporated herein by reference. The hydroxymethyl precussors thereof may be oxidized to the formula (II) aldehyde compounds by treatment with a suitable reagent, such as anhydrous chromic acid-silica gel in tetrahydrofuran or, preferably, with activated magnese dioxide, in a suitable solvent, such as benzene, or, preferably, methylene chloride.

Methods for preparing pyrroles of formula (II) which are the precussors to formula (1) and (2) compounds, respectively, are detailed in EP Publication No. 323 841.

Methods for preparing aminopyrimidines and aminopyridines of formula (II) which are precussors to formula (3) and (4) compounds, respectively, are detailed in EP Publication No. 475 206.

Methods for preparing oxypyridines of formula (II) which are precussors to formula (5) compounds are detailed in EP Publication No. 453 210.

Methods for preparing dihydropyrimidines of formula (II) which are precussors to formula (6) and (7) compounds are detailed in EP Publication No. 481 448.

Methods for preparing pyrazoles of formula (II) which are precussors to formula (8) compounds are detailed in PCT Publication No. WO 91/15479.

It should be appreciated by those skilled in the art that the A^1 - A^6 ring substituted by a R^1-$(CH_2)_n$-group and a substituted acrylic acid group are prepared by processes analogous to those detailed in U.S. Patent No. 5,185,351. Reference should be made to such patent for its disclosure, which is incorporated herein by reference.

Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

Pharmaceutically acceptable base addition salts of compounds of Formula (I) are prepared by known methods from organic and inorganic bases, including nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, meglumine, choline, diethanolamine, and tromethamine.

Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by in vitro and in vivo methods. In vitro antagonist activity is determined by the ability of the compounds to compete with ^{125}I-angiotensin II for binding to vascular angiotensin II receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. In vivo activity is evaluated by the efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

Binding

The radioligand binding assay is a modification of a method previously described in detail (Gunther et al., Circ. Res. 47:278, 1980). A particular fraction from rat mesenteric arteries is incubated in Tris buffer with 80 pM of ^{125}I-angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound ^{125}I-angiotensin II trapped on the filter is quantitated with a gamma counter. The potency of angiotensin II antagonists is expressed as the IC_{50} which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II.

Aorta

The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K_B) are calculated by the dose ratio method using the mean effective concentrations.

Inhibition of pressor response to angiotensin II in conscious rats

Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al., Kidney Int. 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of the control response to angiotensin II (IC_{50}) is used to estimate the potency of the compounds.

Antihypertensive activity

The antihypertensive activity of the compounds is measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., J. Pharmacol. Exp. Ther. 208:310, 1979). Renal artery ligated rats are prepared with indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC_{30}) is used as an estimate of potency.

The intraocular pressure lowering effects employed in this invention may be measured by the procedure described by Watkins, et al., J. Ocular Pharmacol., 1 (2):161-168 (1985).

The compounds of Formula (I) are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule,

sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

For topical ophthalmolgic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quarternary ammonium compounds; buffering ingredients, such as alkali metal chloride; antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

Doses of the compounds of Formula (I) in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of .01 - 200 mg/kg of active compound, preferably 1 - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and convenient for the patient. Topical formulations contain the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 mg, is applied to the human eye.

The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such

antagonism an effective amount of a compound of Formula (I). The method of this invention of producing antihypertensive activity and the method of treating congestive heart failure, glaucoma, and renal failure comprise administering a compound of Formula (I) to a subject in need thereof an effective amount to produce said activity.

Contemplated equivalents of Formula (I) compounds are compounds otherwise corresponding thereto wherein substituents have been added to any of the unsubstituted positions of the Formula (I) compounds provided such compounds have the pharmaceutical utility of Formula (I) compounds.

The following examples illustrate preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as defined hereinabove and as claimed below.

Example 1

(E)-5-n-Butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic Acid

Method A

(i) methyl (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoate

To a suspension of sodium hydride (69 mg, 2.87 mmol) in glyme (5 mL) is added dropwise a solution of trimethyl 3-(2-thienyl)-2-phosphonopropionate (U.S. Patent No. 5,185,351) in glyme (3 mL) under an atmosphere of argon. When the gas evolution has subsided, the mixture is heated to 50°C for 15 minutes. A solution of 5-n-butyl-1-(4-carboxomethoxphenyl)methyl]pyrrole-2-carboxaldehyde (1.92 mmol, prepared in an analogous manner to that disclosed in EP Publication No. 323 841, replacing t-butyl 4'-bromomethylbiphenyl-2-carboxylate with 4-carbomethoxybenzyl bromide) in glyme (3 mL) is added, and the mixture is stirred at 60-65°C for 5 hours. The cooled reaction is partitioned between water and ethyl acetate, and the organic layer is washed with water, dried, concentrated and flash chromatographed over silica gel to give methyl (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoate.

(ii) (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid

A solution of methyl (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]-pyrrole-2-(2-thienyl)methyl-2-propenoate (0.783 mmol) in ethanol (10 mL) is treated with

10% sodium hydroxide solution (4 mL), and the solution is stirred for 3 hours at 25°C. The pH is adjusted to 5 and a solid precipitates. The mixture is diluted with water, cooled and filtered to provide (E)-5-n-butyl-1-[(4-carboxyphenyl)-methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid

Method B

(i) methyl 5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-3-hydroxy-2-(2-thienyl)methylpropanoate

To a solution of diisopropylamine (1.96 g, 0.0194 mol) in dry tetrahydrofuran (40 mL) held at -78°C under argon is added n-butyl lithium (7.3 mL, 0.0183 mol of 2.5 M in toluene), and the mixture is stirred for 10 minutes. Then, methyl 3-(2-thienyl)propanoate (2.83 g, 0.0166 mol) in tetrahydrofuran (2 mL) is added, and the mixture is stirred for 30 minutes at -78°C. A solution of methyl (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoate (0.0111 mol) in tetrahydrofuran (4 mL) is added, and the resulting mixture is stirred at -78°C for 30 minutes. The reaction is partitioned between saturated ammonium chloride solution and ether, the organic extract is washed with brine, dried over anhydrous magnesium sulfate and concentrated to give methyl 5-n-butyl-1-[(4-carboxypheny)lmethyl]pyrrole-3-hydroxy-2-(2-thienyl)-methylpropanoate.

(ii) methyl 5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-3-acetoxy-2-(2-thienyl)methylpropanoate

A solution of methyl 5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-3-hydroxy-2-(2-thienyl)methylpropanoate (9.02 mmol) in methylene chloride (100 mL) is treated with 4-dimethylaminopyridine (0.386g, 3.16 mmol). Then acetic anhydride (8.5 mL, 9.02 mmol) is added dropwise to the stirred mixture. The mixture is stirred for 18 hours, water (35 mL) is added, the mixture is stirred for 1 hour and then diluted with ether and saturated sodium bicarbonate solution. The ether layer is washed with brine, dried with anhydrous magnesium sulfate and evaporated to give the title 3-acetoxy derivative.

(iii) methyl (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoate

A mixture of methyl methyl 5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-3-acetoxy-2-(2-thienyl)methylpropanoate (8.92 mmol) in dry toluene (80 mL) is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.2 mL, 21.4 mmol), and the resulting solution is heated at 80°C under argon for 3 hours. The solvent is evaporated, the residue triturated with ether and activated charcoal is added. After filtration, the filtrate is concentrated to give methyl (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoate.

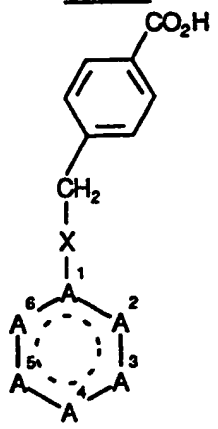
(iv) (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid

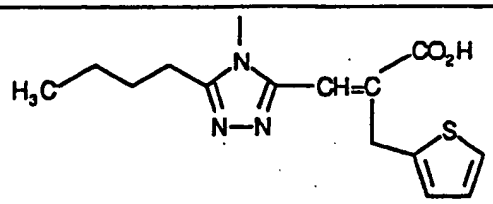
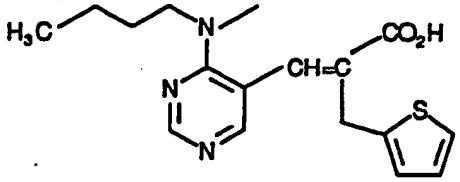
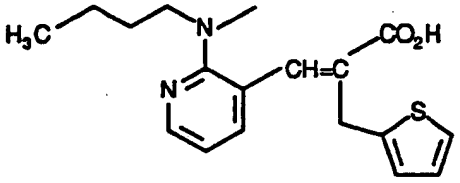
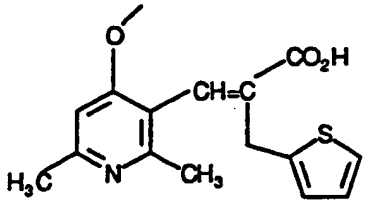
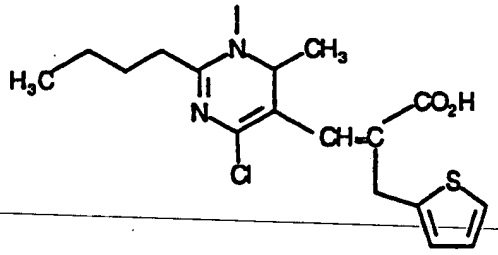
Basic hydrolysis of the above ester (6.71 mmol) according to Method A (ii) gives (E)-5-n-butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid.

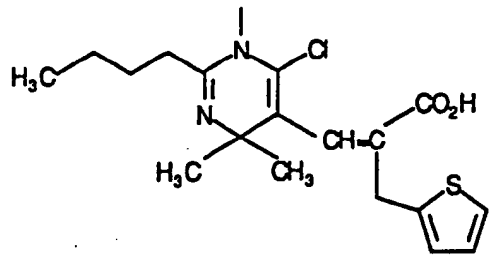
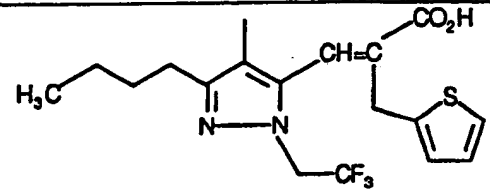
Examples 2-8

Examples 2-8 in Table I are prepared following the proceure of Example 1, replacing 5-n-butyl-1-(4-carboxomethyoxphenyl)methyl]pyrrole-2-carboxaldehyde with the appropriate Formula (II) heterocyclic aldehyde compounds. (See the specification on page 10 for the preparation of these aldehydes).

Table I



EXAMPLE	A^1-A^6 RING PRODUCT
2	 (In Exmple 2, as shown, X is a covalent bond.)
3	 (In Example 3, as shown, X is -N(R^9)-, wherein R^9 is n-butyl.)
4	 (In Example 4, as shown, X is -N(R^9)-, wherein R^9 is n-butyl.)
5	 (In Example 5, as shown, X is -O-.)
6	 (In Example 6, as shown, X is a covalent bond.)

7	 (In Example 7, as shown, X is a covalent bond.)
8	 (In Example 8, as shown, X is a covalent bond.)

Example 9

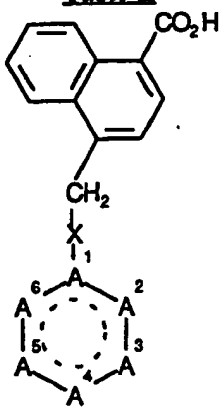
(E)-5-n-Butyl-1-[(4-carboxynaphthyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic Acid

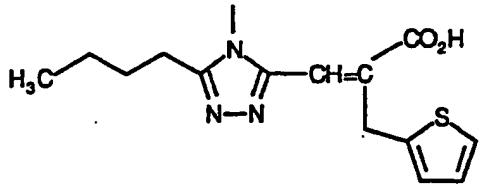
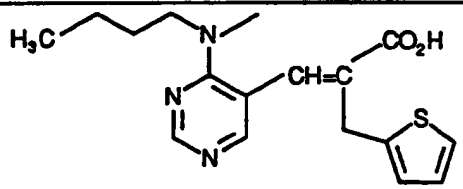
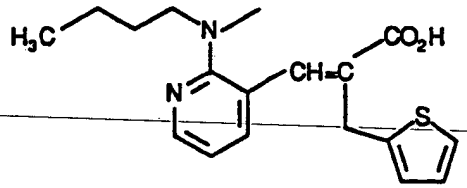
The procedure of Example 1 is followed replacing 5-n-butyl-1-(4-carboxomethoxphenyl)methyl]pyrrole-2-carboxaldehyde with 5-n-butyl-1-[(4-carbomethoxynaphthyl)methyl]pyrrole-2-carboxaldehyde, which is prepared by the methods disclosed in EP Publication No. 323 841, replacing t-butyl 4'-bromomethylbiphenyl-2-carboxylate with methyl 4-bromomethylnaphthalene-1-carboxylate (Can J. Chem., 59:2629 (1981)).

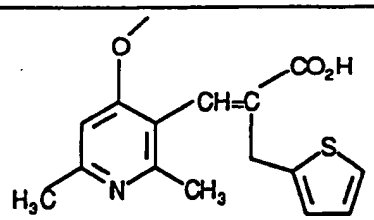
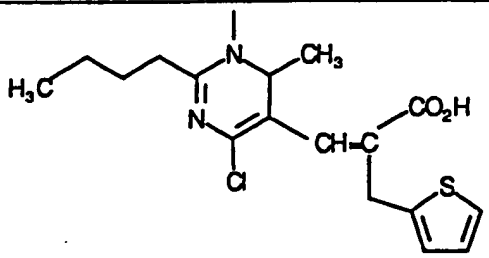
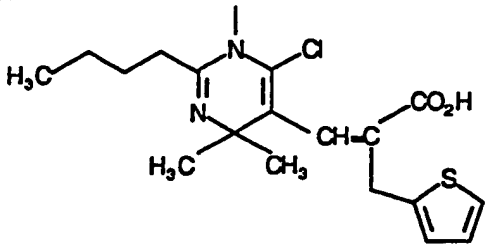
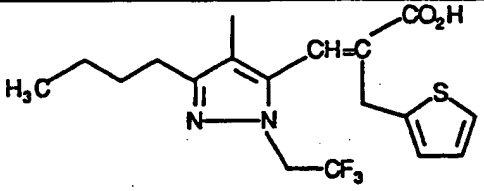
Examples 10-16

Examples 10-16 in Table II are prepared following the procedure of Example 9, replacing 5-n-butyl-1-(4-carboxomethyoxphenyl)methyl]pyrrole-2-carboxaldehyde with the appropriate Formula (II) heterocyclic aldehyde compounds

Table II



Example	A^1-A^6 RING PRODUCT
10	 (In Exmple 10, as shown, X is a covalent bond.)
11	 (In Example 11, as shown, X is -N(R^9)-, wherein R^9 is n-butyl.)
12	 (In Example 12, as shown, X is -N(R^9)-, wherein R^9 is n-butyl.)

13	 (In Example 13, as shown, X is -O-.)
14	 (In Example 14, as shown, X is a covalent bond.)
15	 (In Example 15, as shown, X is a covalent bond.)
16	 (In Example 16, as shown, X is a covalent bond.)

Example 17

An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

Ingredients	Amounts
(E)-5-n-butyl-1-[(4-carboxyphenyl)-methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid	100mg
magnesium stearate	10 mg
lactose	100 mg

Example 18

The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Ingredients	Amounts
(E)-5-n-butyl-1-[(4-carboxynaphthyl)-methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid	75 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Example 19

(E)-5-n-Butyl-1-[(4-carboxyphenyl)methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid, 50 mg, is dispersed in 25 mL of normal saline to prepare an injectable preparation.

Example 20

A topical opthamological solution for administering Formula (I) compounds is produced by mixing under sterile conditions the ingredients in proportions, for example, as shown below.

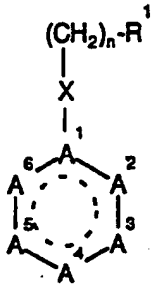
Ingredients	Amounts (mg/mL)
(E)-5-n-butyl-1-[(4-carboxynaphthyl)-methyl]pyrrole-2-(2-thienyl)methyl-2-propenoic acid	1.0
dibasic sodium phosphate	10.4
monobasic sodium phosphate	2.4
chlorobutanol	5.0
hydroxypropanol methylcellulose	5.0
sterile water	q.s.ad 1.0mL
1.0 N sodium hydroxide	q.s.ad pH 7.4

It is to be understood that the invention is not limited to the embodiments illustrated hereabove and the right to the illustrated embodiments and all modifications coming within the scope of the following claims is reserved.

5

What is claimed is:

1. A compound of the formula:



wherein:

R^1 is phenyl or naphthyl, each of which is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_{1-6}alkyl, NO_2, CF_3, Q-CO_2R', tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR', $NHSO_2R''$, SO_3H, CONR'R', CN, SO_2C_{1-6}alkyl, NR'R', NR'COH, NR'COC_{1-6}alkyl or NR'CO-phenyl;

n is 0-4;

A^1 is C or N when X is a covalent bond, or C when X is other than a covalent bond;

A^2 is CR^2, CR^{14}, or $C{=}R^3$;

A^3 is CR^2, CR^4, N, or NR^{15};

A^4 is CR^5, CR^5R^9, or N;

A^5 is absent or present as CR^6 or N;

A^6 is CR^7 when A^5 is absent or CR^8 or N when A^5 is present;

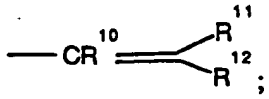
with the proviso that:

(1) one of A^2 or A^3 is CR^2; and

(2) at least one, but not more than three of A^1, A^3, A^4, A^5 and A^6 are N;

each R' independently is H or C_{1-6}alkyl;

R" is R', C_mF_{2m+1}, wherein m is 1-3, or phenyl which is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_{1-6}alkyl, NO_2, CF_3, Q-CO_2R', tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR', $NHSO_2R'$, SO_3H, CONR'R', CN, SO_2C_{1-6}alkyl, NR'R', NR'COH, NR'COC_{1-6}alkyl or NR'CO-phenyl;

R^2 is  ;

R^3 is O, (H,H), or (H, C_{1-4}alkyl);

R^4 is H, C_{1-4}alkyl, Cl, Br, F, or I;

R^5 is H, C_{1-4}alkyl, Cl, Br, F, or I;

R^6 is H or C_{1-4}alkyl;

R^7 is C_{2-8}alkyl, SC_{1-7}alkyl or OC_{1-7}alkyl;

R^8 is H, C_{2-8}alkyl, SC_{1-7}alkyl, or OC_{1-7}alkyl;

each R^9 independently is H or C_{1-6}alkyl;

R^{10} is H or C_{1-6}alkyl;

R^{11} is CO_2R', CONR'R', tetrazolyl, or SO_2NH_2;

R^{12} is C_1-C_6alkyl, phenyl-Y-, biphenyl-Y-, naphthyl-Y-, 2- or 3-thienyl-Y-, 2- or 3-furanyl-Y-, 2-, 3- or 4-pyridyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, or tetrazolyl-Y-, with each heteroaryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR'R', CO_2R', SO_2NHR', SO_3H, CONR'R', OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR'COH, or NR'COC_1-C_6alkyl and with each aryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CF_3, NR'R', CO_2R', SO_2NHR', SO_3H, CONR'R', OH, NO_2, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, NR'COH, or NR'COC_1-C_6alkyl or with each aryl group being substituted by methylenedioxy, phenoxy, or phenyl;

Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched optionally substituted by phenyl or benzyl, wherein each phenyl or benzyl group is unsubstituted or substituted by Cl, Br, F, I, NO_2, CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, CN, or CO_2R';

Q is -CH=CH-, -$(CH_2)_{0-4}$-, -X-$(CH_2)_{1-2}$-U-$(CH_2)_{1-2}$-, or -V-CH(R^{13})-;

X is a covalent bond, -O-, -S-, or -N(R^9)-;

U is absent or present as -O-, -S-, or -N(R^9)-;

V is -O-, -S-, or -N(R^9)-;

R^{13} is H, phenyl, or benzyl wherein each phenyl or benzyl group is unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_{1-6}alkyl, NO_2, CF_3, Q-CO_2R', tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR', $NHSO_2R''$, SO_3H, CONR'R', CN, SO_2C_{1-6}alkyl, NR'R', NR'COH, NR'COC_{1-6}alkyl or NR'CO-phenyl;

R^{14} is Cl, Br, F, r I; and

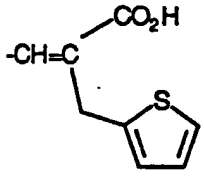
R^{15} is H, C_{1-6}alkyl, -$(CH_2)_{1-2}C_{3-6}$cycloalkyl, -$(CH_2)_{1-2}CF_3$, or -$(CH_2)_{0-2}$phenyl, wherein the phenyl is unsubstituted r substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein R^1 is phenyl or naphthyl, each of which is substituted by Q-CO_2R', CONR'R', $NHSO_2R''$, or tetrazolyl.

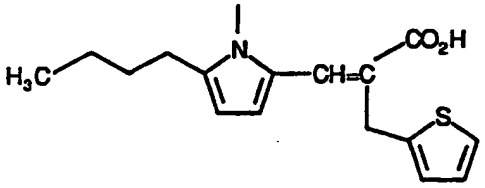
3. The compound according to claim 2 wherein R^1 is phenyl or naphthyl, each of which is substituted by 4-CO_2H, and n is 1.

4. The compound according to claim 3 wherein R^2 is

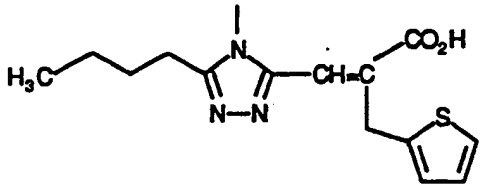


in which the A^1 - A^6 ring and the CO_2H group are trans to each other.

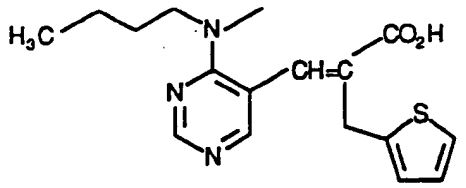
5. The compound according to claim 4 wherein A^1 - A^6 and X are



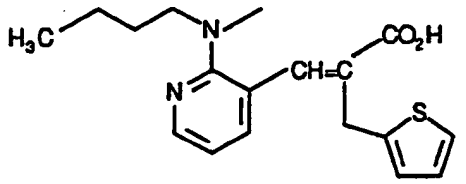
6. The compound according to claim 4 wherein A^1-A^6 and X are



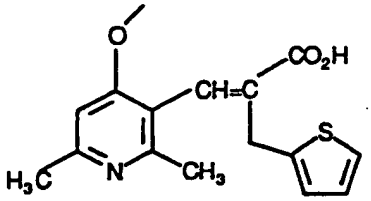
7. The compound according to claim 4 wherein A^1 - A^6 and X are



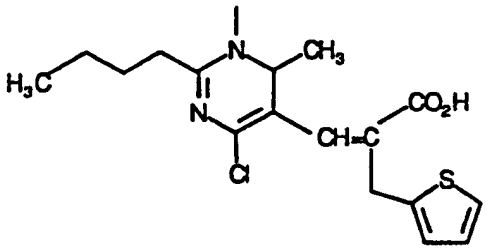
8. The compound according to claim 4 wherein A^1 - A^6 and X are



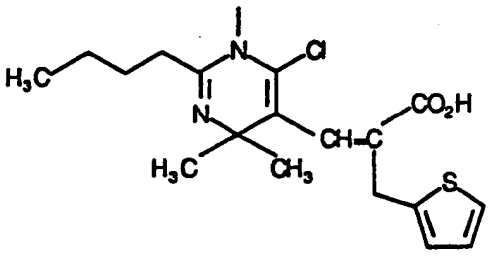
9. The compound according to claim 4 wherein A^1 - A^6 and X are



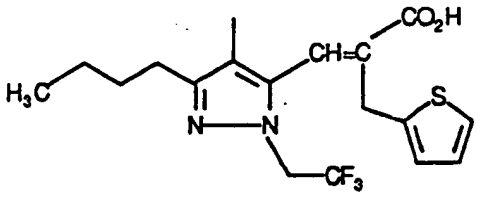
10. The compound according to claim 4 wherein A^1 - A^6 and X are



11. The compound according to claim 4 wherein A^1 - A^6 and X are



12. The compound according to claim 4 wherein A^1 - A^6 and X are



13. A pharmaceutical composition comprising a pharmaceutical carrier and a compound of claim 1.

14. A method of antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

15. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

16. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

17. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

18. A method of treating glaucoma which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/03478

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,053,073 (ANTHONY ET.AL.) 01 OCTOBER 1991, SEE TABLES 1 THROUGH 6.	1-4,8,9,13-18
A	US,A, 4,792,567 (BURKART ET.AL.) 20 DECEMBER 1988, SEE COLUMNS 1 AND 2.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 JULY 1994	Date of mailing of the international search report AUG 01 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Y.N, Gupta Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US94/03478

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4,8,9 AND 13-18

Remark n Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/US94/03478

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

CO7D 213/02,401/06,405/06,409/06,411/06,413/06; A61K 31/44

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/340,341,342,343,345,352,357; 546/255,275,276,277,278,280,281,284,
290,297,298,300,301,302,304,307,329,334,335,336,
337,338

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/340,341,342,343,345,352,357;
546/255,275,276,277,278,280,281,284,290,297,298,300,301,302,304,307,329,334,335,336,
337,338

B. FIELDS SEARCHED
Documentation other than minimum documentation that are included in the fields searched:

JOURNAL OF ORGANIC CHEMISTRY

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. CLAIMS 1-4,8,9 AND 13-18 DRAWN TO COMPOUNDS, COMPOSITION AND METHOD OF USE WHEN RING A1-A6 IS PYRIDINE.

II. CLAIMS 1-5 AND 13-18 DRAWN TO COMPOUNDS COMPOSITION AND METHOD OF USE WHEN RING A1-A6 IS PYRROLE.

III. CLAIMS1-4,6 AND 13-18 DRAWN TO COMPOUNDS COMPOSITION AND METHOD OF USE WHEN RING A1-A6 IS 1,3,4-TRIAZOLE.

IV. CLAIMS 1-4, 7,10,11 AND 13-18 DRAWN TO COMPOUNDS, COMPOSITION AND METHOD OF USE WHEN A1-A6 IS PYRIMIDINE.

INVENTIONS I-IV ARE DRAWN TO THE STUCTURALLY DIFFERENT COMPOUNDS AND INVENTIONS I-IV ARE DEEMED TO BE DISTINCT UNDER PCT RULE 13.2, AND THUS LACKS THE UNITY OF INVENTION.